

## Cancer Related Fatigue: Diagnosis and Rehabilitation

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### Abstract

Cancer related fatigue (CRF) is a distressing and persistent exhaustion, affecting 30% to 60% of cancer patients during treatment and around 20% to 30 % post-treatment. It is an underdiagnosed and undertreated condition in most cases. Diagnosis is usually made by clinical screening using numeric rating scales and patient reported outcomes, though none are adapted for Low Middle-Income Countries (LMIC) like Pakistan. Evidence-based rehabilitation techniques for CRF include aerobic and resistance exercise, Mind-body therapies, Cognitive behavioural therapy, telerehabilitation, and pharmacological interventions. However, implementation of these strategies in the LMIC is limited due to shortage of trained rehabilitation professionals, absence of LMIC relevant protocols, inadequate referrals, low patient education and lack of clinical guidelines for CRF. This mini review summarizes the current approaches for diagnosis and rehabilitation of CRF. We have identified the challenges and offer some practical strategies for integration of CRF rehabilitation cancer care framework in LMIC including Pakistan.

**Keywords:** Cancer Related Fatigue; Cancer Rehabilitation; Outcome measures Assessment tools; Exercise intervention; LMIC; Pakistan

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### Introduction

National Comprehensive Cancer Network (NCCN) USA defines Cancer-related fatigue (CRF) as a distressing, persistent sense of physical, emotional, and/or cognitive exhaustion related to cancer that is not proportional to activity and interferes with functioning. An estimated 30% to 60% patients experience CRF during treatment, and 20% to 30 % develop it post-treatment. Patients with co-existing anaemia, endocrine dysfunction, neuromuscular complications, psychological distress, and end-organ dysfunction are more prone to developing CRF.<sup>1,2</sup> In lower-middle-income countries, CRF is highly prevalent and is complicated by late-stage presentation, limited supportive

care, and resources.<sup>3</sup> CRF can have debilitating effect on quality of life and may result in patient's non-compliance with treatment. Early recognition of CRF and implementing appropriate rehabilitation strategies are important steps in ensuring holistic cancer care.<sup>2</sup> This mini-review summarizes the current literature on the diagnosis, assessment, and rehabilitation of CRF

### Mechanistic Insights into CRF

CRF occurs due to complex interactions between biological, psychological, and treatment-related factors. Inflammatory and immune variables are closely associated with CRF, with elevated circulating inflammatory markers, and increased NF- $\kappa$ B in patients. Disruption in the hypothalamic-pituitary-adrenocortical axis also results in fatigue through the release of glucocorticoids. Mitochondrial deficits likely contribute to reduced energy availability, resulting in fatigue.<sup>4</sup>

Cancer therapies (surgery, chemotherapy, radiation therapy, endocrine therapy, and biologic response modifier therapy) can cause CRF by direct tissue injury, neuropathy, inflammation and immune responses.<sup>2</sup> Psychiatric disorders such as Anxiety and depression, and cognitive Impairment, such as decreased attention span and impaired perception, trigger the onset in predisposed patients or worsen fatigue in those already affected. Sleep disturbances and circadian rhythm disruption can also exacerbate CRF.<sup>2</sup>

Recently, the 3P-factor model has been proposed to describe the etiology of CRF. Predisposing factors (e.g., age, genetics, psychological distress), precipitating factors (e.g., cancer or its treatment-induced inflammation) and perpetuating factors (e.g., poor sleep, physical inactivity, and poor diet) collectively contribute to its presence and severity. Screening of these factors can enable interventions to prevent or mitigate the severity of CRF.<sup>5</sup>

### Diagnosis of CRF

There is a lack of any universally accepted objective diagnostic criteria, however, the following criteria are being used to establish a diagnosis.

### Clinical criteria

The NCCN guidelines recommend using a numeric rating scale (NRS, 0-10) for routine screening of fatigue, with scores of  $\geq 4$  requiring management. The patient-reported

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outcomes (PROs) measures, such as the Functional Assessment of Cancer Therapy-Fatigue (FACT-F), Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue), Multidimensional Fatigue Inventory (MFI) and Brief Fatigue Inventory (BFI), are commonly used to assess the severity and impact of fatigue. (Table 1) A comprehensive history of comorbidities, medication, therapies, sleep, mood, anaemia and other risk factors also facilitates diagnosis.<sup>6-8</sup>

However, all these questionnaires are validated in the Western Caucasian population and require adaptation and validation to be used in LMIC like Pakistan.

Inflammatory and other biomarkers have shown predictive value for CRF, but are costly and their results are not yet definitive.<sup>9</sup> A more feasible approach can be the use of electronic activity monitoring devices or websites that can flag worsening fatigue and trigger timely intervention using predefined algorithms. Such systems are cost-effective and portable, however, worldwide adoption is limited.<sup>10</sup>

### Rehabilitation of CRF

There are many evidence-based rehabilitations strategies to manage CRF. We will discuss some of these.

### Exercise-based Interventions

Physical activity-based rehabilitation is the most common intervention used for CRF and is recommended by NCCN, ASCO and ESMO guidelines.<sup>1,8,11</sup> Both aerobic and anaerobic (resistance training) exercises have shown benefits in relieving fatigue. Aerobic exercise is more effective in improving QoL and is more beneficial to female cancer patients.<sup>12</sup>

Mind-body exercises such as Yoga, Qigong, and Tai chi also improve balance, flexibility, muscle strength, and overall health in CRF. These exercises use meditation with

controlled breathing and mental focussing to achieve relaxation.<sup>2</sup>

### Psychological and Behavioural Interventions

Psychosocial interventions such as mindfulness-based stress reduction techniques, psychosocial support, and cognitive behavioural therapy (CBT) have demonstrated effectiveness in alleviating various physical and mental complications associated with cancer. CBT interventions include a range of psychotherapeutic techniques aimed at addressing maladaptive behaviours and psychological distress through cognitive and behavioural modifications.<sup>13</sup>

Therapist-guided eHealth and apps that combine psychoeducation, activity pacing, sleep strategies, mindfulness, and CBT content have shown symptom reduction and are feasible in a variety of settings including LMIC. The Untire app is one example that uses this approach.<sup>14</sup>

### Pharmacological intervention

Short term corticosteroids (e.g., Dexamethasone and Methylprednisolone) may improve QoL and are recommended by NCCN and ESMO guidelines.<sup>8,11</sup> Psychostimulants like methylphenidate may be used with caution in consideration with other modifiable causes.<sup>8</sup> Supplements for anaemia can be used as supportive treatment.<sup>2</sup> Antidepressants, hypnotics and acetylcholinesterase inhibitors are not recommended for CRF.<sup>2,11</sup>

### Multidisciplinary Rehabilitation

CRF varies from person to person, and needs a personalized, multidimensional interventions. A functional rehabilitation and exercise programme provided by an interdisciplinary team including oncologists, rehabilitation medicine physicians, rehabilitation nurse, occupational therapists, and physiotherapists can significantly reduce fatigue symptoms.

**Table:** Commonly used Cancer-Related Fatigue Assessment Tools in Clinical and Research Settings.

| Screening tool             | Response scale                                                                                 | Number of items                                                                | Recall period                               | Type of fatigue domain                                                                                                 |
|----------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Numeric rating scale (NRS) | Numeric rating scale (0-10), where 0 is "no fatigue" and 10 is "the worst fatigue imaginable." | 1 item                                                                         | Adaptable, "past 7 days" in NCCN guidelines | Assesses severity only; Does not differentiate between domains                                                         |
| BFI                        | Numeric rating scales (0-10)                                                                   | 9 items (3 items assess fatigue, 6 items assess interference with daily life.) | Past week and past 24 h                     | Assesses Severity and Interference (used for quick assessment)                                                         |
| MFI                        | 5-point Likert scale                                                                           | 20 items                                                                       | "in the past few days."                     | Multidimensional (5 domains): General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation, Reduced Activity. |
| FACT-F/ FACIT-F            | 5-point Likert scale                                                                           | 13 items                                                                       | "Past 7 days."                              | Impact on Function and QoL                                                                                             |
| EORTC QLQ-FA12             | 4-point Likert                                                                                 | 12                                                                             | Past week                                   | 5 (physical, emotional, cognitive)                                                                                     |

### Technology-Based Rehabilitation

Telerehabilitation over video or app platforms is safe and feasible, with potential for positive effects on fatigue and health-related QOL.<sup>15</sup> Telerehabilitation may overcome barriers related to in-person care delivery. Mobile applications, wearables, and virtual reality platforms enable remote monitoring, personalized feedback, progress tracking, and symptom management in real time.<sup>15</sup>

### Alternative and Complementary Interventions

NCCN suggests the use of nutritional consultation, adequate hydration, and electrolyte balance may help reduce fatigue. Bright white light therapy (a traditional Chinese medicine therapy of exposing patients to high fluorescent light), and acupuncture may also be used as supportive care.<sup>1,8</sup>

### Implementation Challenges related to CRF Rehabilitation

Patients with cancer diagnosis in High-income countries have better survival despite having a higher incidence. This can be attributed to advanced treatment and high-quality follow-up care. In contrast, LMICs like Pakistan face higher mortality despite having lower incidences. This is due to a lack of public awareness about cancer, delay in diagnosis, non-availability of advanced interventions and barriers in implementing supportive care.

Specialized cancer centers are limited to major cities only and in many of the existing facilities have inadequate staff and facilities to deal with high patient loads. Thus, leaving little time for CRF screening and referral.

Shortage of trained rehabilitation medicine physicians, physiotherapists, psychologists, and occupational therapists limit implementation of CRF rehabilitation protocols. Most oncologists are unaware of rehabilitation importance or lack referrals to provide care.

Patient related barriers include financial strain, distance, limited literacy and belief that fatigue is an unavoidable part of treatment. Hence, patients may not seek rehabilitation or are unable to maintain adherence to interventions.

National policies for cancer management rarely include rehabilitation or fatigue management. The guidelines come from research in high-income countries where supportive care facilities are already available and not adapted for the local population.<sup>3,16</sup>

### Future Directions

National Cancer care policies should include CRF screening and rehabilitation, with funds allocated for facilities and staff training. Patients should be educated about the availability and value of cancer rehabilitation and strategies to reduce fatigue.

More precise rehabilitation techniques will likely combine symptoms with biologic and behavioral markers to adapt the treatment for each patient. Research should test newer and possibly lifelong interventions such as chronotherapy, microbiome-modulating strategies, and neuromodulation alongside standard rehabilitation for more effective

strategies.<sup>16</sup>

### Conclusion

Cancer-related fatigue is a common, persistent, distressing exhaustion related to cancer. Diagnosis can be made using NCCN or ASCO criteria or by accessing PROs. Rehabilitation interventions include structured exercise, behavioural therapy, integrative therapies, and technology-enabled delivery. However, lack of professionals, resources, and funds, along with patient-related barriers, make it difficult to implement it in LMIC. An appropriate system for follow-up care is essential.

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